

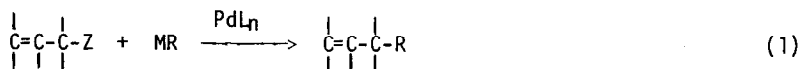
SCOPE OF THE PALLADIUM-CATALYZED COUPLING REACTION OF ORGANOMETALLICS
 WITH ALLYLIC ELECTROPHILES. EFFECT OF THE LEAVING GROUP¹

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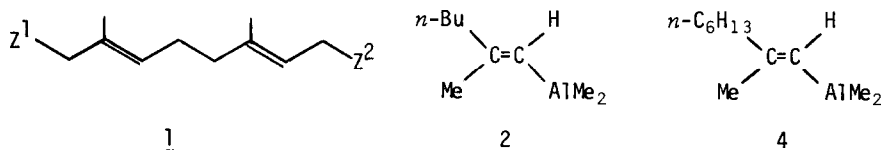
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SUMMARY: Various allyl alcohol derivatives containing OAlR₂, OPO(OR)₂, and OSiR₃ groups, in addition to allylic halides and acetates, participate in the Pd-catalyzed coupling reaction with alkenyl- and arylmetals, such as those containing Al, Zn and Zr, to give the corresponding cross-coupled products, the order of their reactivity being: halogen, OAc > OAlR₂ > OPO(OR)₂ > OSiR₃.

We wish to report that the Pd-catalyzed coupling reaction of organometallics, such as those containing Al, Zn, and Zr, with allylic electrophiles we described recently⁴ is highly general with respect to the leaving group of the allylic derivatives. Thus, in addition to allylic halides and acetates,⁴ various alcohol derivatives containing OAlR₂ (e.g., R = Me), OPO(OR)₂ (e.g., R = Et), and OSiR₃ (e.g., SiR₃ = SiMe₃ or SiMe₂Bu-*t*) groups can participate in the reaction, the order of their reactivity being: halogen, OAc > OAlR₂ > OPO(OR)₂ > OSiR₃.



Z = halogen, OAc, OAlR₂, OPO(OR)₂, or OSiR₃

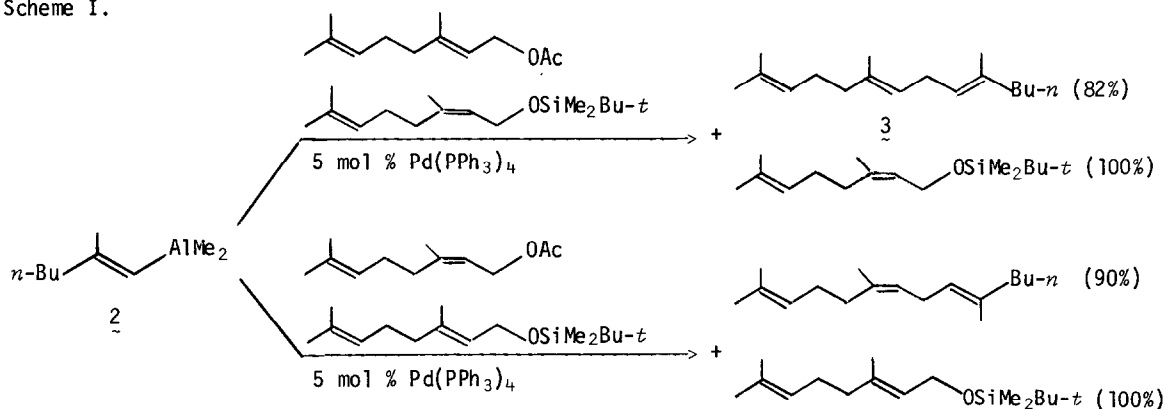


In connection with our study directed toward the synthesis of long chain terpenoids, it became desirable to cleanly differentiate two allylic groups of bisallylic derivatives, e.g., 1, in their cross-coupling reaction. With this objective in mind we prepared a series of geranyl and neryl derivatives and examined their reaction with (*E*)-(2-methyl-1-hexenyl)dimethylalane⁵ (2) in the presence of 5 mol % of Pd(PPh₃)₄, which was carried out in essentially the same manner as described previously.⁴ For each case a control experiment was carried out in the absence of Pd(PPh₃)₄ to ascertain if the Pd catalyst was indeed required.

As summarized in Table I, all geraniol derivatives we have so far tested, i.e., those containing Cl, OAc, OAlMe₂, OPO(OEt)₂, OSiMe₃, and OSiMe₂Bu-*t* groups, react with 2 to give (6*E*,9*E*)-2,6,10-trimethyl-2,6,9-tetradecatriene⁶ (3) of $\geq 98\%$ stereoisomeric purity. Although geranyl phosphate reacts with 2 to give 3 in modest yield (50-60%) even in the absence of Pd(PPh₃)₄, none of the other derivatives reacts with 2 in the absence of Pd catalyst.

The relative rates of the reactions of these allylic derivatives with 2 were determined by following the reactions with time (Table I). Although the results are somewhat erratic, the order of their reactivity based on the product yields after 1 hr is: Cl, OAc > OAlMe₂ > OPO(OEt)₂ > OSiR₃ (SiR₃ = SiMe₃ or SiMe₂Bu-*t*). These results suggested that it might be feasible to cleanly react allylic chlorides or acetates in the presence of less reactive allylic derivatives. To probe this matter in a practically meaningful manner, we reacted the alkenylalane 2 with a 1:1 mixture of geranyl acetate and neryl *t*-butyldimethylsilyl ether as well as with a 1:1 mixture of neryl acetate and geranyl *t*-butyldimethylsilyl ether in the presence of 5 mol % of Pd(PPh₃)₄. We were gratified to find that, in each case, the acetate reacted cleanly to give the corresponding cross-coupled product contaminated with no more than a trace (< 1-2%) of its stereoisomer which could be formed by the reaction of the silyl ether (Scheme I). Very similar results were obtained with a 1:1 mixture of geranyl chloride and neryl *t*-butyldimethylsilyl ether. Application of these findings to the reaction of bisallylic derivatives, e.g., 1, is under investigation.

Scheme I.



Secondary allyl derivatives, such as 2-cyclohexenyl acetate, and γ -monosubstituted primary allyl derivatives, such as (*E*)-crotyl acetate, also readily participate in the coupling reaction. In the Pd-catalyzed reaction of (*E*)-crotyl acetate with (*E*)-2-methyl-1-octenyldimethylalane (4), however, the coupling products consist of an 80:10:10 mixture⁷ of 5, 6, and 7.

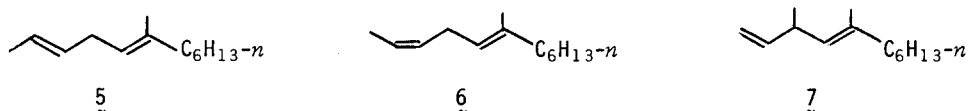


Table I. The Pd-Catalyzed Reaction of Geranyl Derivatives with (*E*)-2-Methyl-1-hexenyldimethylalane ^a

| Leaving group (Z) of geranyl derivative (C ₁₀ H ₁₇ Z) | Yield ^b (%) of 3 | | |
|---|------------------------------------|-----------------|-------|
| | 1 hr | 6 hr | 48 hr |
| Cl ^c | 100 | - | - |
| OAc ^d | 100 | - | - |
| OAlMe ₂ ^e | 43 | 93 | 100 |
| OPO(OEt) ₂ ^f | 33 | 43 ^g | - |
| OSiMe ₃ ^h | 18 | 41 | 94 |
| OSiMe ₂ Bu- <i>t</i> ⁱ | - | 37 | 46 |

^aThe reaction is carried out in THF at room temperature using a geranyl derivative (C₁₀H₁₇Z) and **2** in a 1:1 molar ratio and 5 mol % of Pd(PPh₃)₄ as a catalyst. ^b By GLC. ^c Prepared by the method described by Calzada and Hooz: J. G. Calzada and J. Hooz, *Org. Synth.* 54, 63 (1974). ^d Prepared by treating geraniol with 2.5 equivalents each of Ac₂O and pyridine. ^e Generated *in situ* by treating geraniol with one equivalent of Me₃Al in THF (-78 to 25°C). ^f Prepared in quantitative yield by treating geraniol sequentially with *n*-BuLi (ether, -78°C) and ClPO(OEt)₂ (-78 to 25°C). ^g The reaction proceeds to 50-60% completion even in the absence of Pd(PPh₃)₄. ^h Prepared by treating geraniol sequentially with *n*-BuLi in hexane (-78°C) and Me₃SiCl (1.3 equivalents, THF, -78 to 25°C). ⁱ Prepared in a manner similar to that described above except that *t*-BuMe₂SiCl is used in place of Me₃SiCl.

Table II. The Pd-Catalyzed Reaction of (*E*)-Crotyl Acetate with Phenylmetals ^a

| Metal-containing moiety (M) of phenylmetal (PhM) ^b | Reaction time (hr) | Total yield ^c (%) | Products —Composition (%)— | |
|---|-----------------------|---------------------------------|------------------------------------|-----------------------|
| | | | 1-Phenyl- 2-butene ^d | 3-Phenyl- 1-butene |
| MgBr | 3 | 15 | 48 | 52 |
| ZnCl | 3 | 100 | 77 | 23 |
| CdCl | 12 | 96 | 77 | 23 |
| AlPh ₂ | 3 | 55 | 62 | 38 |
| ZrPh ₃ | 24 | 25 | 46 | 54 |

^a The reaction is carried out in THF at room temperature using (*E*)-crotyl acetate and a phenylmetal derivative in a 1:1 molar ratio and 5 mol % of Pd(PPh₃)₄ as a catalyst. ^b Prepared *in situ* by treating PhMgBr with appropriate amounts of metal halides. ^c By GLC. ^d *E* and *Z* mixtures.

The regiochemistry of the reaction appears to be largely independent of the regiochemistry of the allylic derivative as well as of the nature of the leaving group, as both $\geq 99\%$ pure (*E*)-crotyl acetate and a 72:28 mixture of crotyl chloride (*E* and *Z* isomers) and 3-chloro-1-butene display essentially the same regioselectivity. On the other hand, solvents do affect the regiochemistry. Thus, the Pd-catalyzed reaction of **4** with crotyl acetate in THF (90%), ethyl ether (81%), CH₂Cl₂ (74%), and DMSO (30%) displays the regioselectivity, i.e., (5 + 6)/7, indicated in the parentheses.

We have also examined the effects of metal gegenions in the reaction of (*E*)-crotyl acetate with phenylmetals containing Mg, Zn, Cd, Al, and Zr, and found that metal gegenions significantly affect the regioselectivity as well as the product yield (Table II). Unfortunately, the maximum regioselectivity observed in the reactions of crotyl derivatives with alkenyl- or aryl-metals has been limited to 80-90%. It is worth noting, however, that there is a striking contrast between the regiochemistry observed here with Pd(PPh₃)₄, which favors the carbon-carbon bond formation at the less hindered allylic carbon atom, and that of the Ni-catalyzed reaction of methyl- and phenylmagnesium halides with allylic alcohols of Felkin,⁸ which tends to favor attack at the more highly alkyl-substituted allylic carbon atom.

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7. Professor J. Schwartz of Princeton University has recently informed us of their results obtained in the Pd-catalyzed reaction of alkenylzirconium derivatives with γ -monosubstituted allylic acetates, which show considerably different regiochemistry. For their results obtained in some stoichiometric reactions of π -allylpalladium derivatives, see J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.*, **102**, 7381 (1980).
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